The accomplishments of Embden and Parnas radically reshaped thinking about alcoholic fermentation and muscle glycolysis, making central the linkages between oxidation and energy by construing the process in terms of phosphorylated compounds and proposing the transfer of phosphate to ADP to form ATP. Several years later Fritz Lipmann (1941) would introduce the symbol ~P to designate what he memorably called the "energy-rich phosphate bonds" in ATP (p. 101). Already in the 1930s, though, the connections linking oxidation, phosphates, and energy were becoming apparent. In this respect, an important step was Dorothy Needham's proposal of a second esterification of phosphate in fermentation. She noted that even when fluoride poisons blocked the step from phosphoglyceric acid to phosphopyruvic acid (which by then had been identified as an intermediate before the production of pyruvic acid), free phosphate continued to be taken up into an ester. She also observed that in normal fermentation more phosphocreatine was formed per molecule of lactic acid than the single transfer of phosphate from phosphopyruvic acid to ATP could explain. Accordingly, she proposed a second synthesis of ATP (Needham, 1937), and Negelein and Brömel (1939) demonstrated that this involved first the formation of diphospholgyceric acid (3-phosphoglyceroyl phosphate) as the immediate oxidation product of glyceraldehyde 3-phosphate.

One last change resulted in the conception of the pathway as still accepted today. In 1934 Warburg and Christian found another constituent beyond ATP in a coferment preparation made from red blood cells. In 1935 they identified it chemically as containing nicotinic acid amide (Warburg & Christian, 1935). Soon thereafter they characterized it functionally as a "hydrogen-transporting co-ferment" (Warburg, Christian, & Griese, 1935) and proposed the name *triphosphopyridine nucleotide (TPN)* (Warburg & Christian, 1936). The main purpose of this 1936 article, though, was to announce their isolation of a similar coferment with just two, rather than three, molecules of phosphoric acid per molecule of nicotinamide. They proposed the name *diphosphopyridine nucleotide (DPN)*; this key substance has also been known as *coenzyme I*, *nicotinamide adenine dinucleotide (NAD)*, and, in its oxidized/reduced states, *NAD^+/NADH*.[38] Meyerhof then established that it was actually NAD^+, not

conclusion that this resynthesis does not involve a relationship that might be termed 'energetic coupling,' but more probably involves a transfer of phosphate residues from molecule to molecule" (Parnas et al., 1934, p.68).

[38] More specifically, the two coenzymes ("co-ferments") discovered by Warburg and Christian are pyridine nucleotides that have in common two phosphate-containing nucleotides (nicotinic amide mononucleotide and adenine flavin dinucleotide); however, DPN lacks an additional